

required in labeling by paragraph (e) of this section.

(1) The boxed statement shall appear in (or next to) the information required in brief summary by § 202.1(e)(1) of this chapter and shall have prominence at least equal to that provided for other information presented in the brief summary and shall have type size, captions, color, and other physical characteristics comparable to the information required in the brief summary.

(2) Less-than-effective indication(s) in the promotional message of an advertisement which is a single page or less shall be keyed to the boxed statement by asterisk, by an appropriate statement, or by other suitable means providing adequate emphasis on the boxed statement. On each page where less-than-effective indication(s) appear in a multiple page advertisement, an asterisk shall be placed after the most prominent mention of the indication(s); if the degree of prominence does not vary, an asterisk shall be placed after the first mention of the indication. The asterisk shall refer to a notation at the bottom of the page which shall state "This drug has been evaluated as probably effective (or possibly effective whichever is appropriate) for this indication" and "See Brief Summary" or "See Prescribing Information," the latter legend to be used only if the advertisement carries the required information for professional use as set forth in § 201.100(c)(1).

(3) For less-than-effective indications which are included in the advertisement only as a part of the information required in brief summary, the disclosure information shall appear in this portion of the advertisement in the same manner as is specified for labeling in paragraph (e) of this section.

(g) The Commissioner may find circumstances are such that, while the elimination of claims evaluated as other than effective will generally eliminate the need for disclosure about such claims, there will be instances in which the change in the prescribing or promotional profile of the drug is so substantial as to require a disclosure of the reason for the change so that the purchaser or prescriber is not misled by being left unaware through the sponsor's silence that a basic change

has taken place. The Food and Drug Administration will identify these situations in direct correspondence with the drug promoters, after which the failure to make the disclosure will be regarded as misleading and appropriate action will be taken.

[40 FR 13998, Mar. 27, 1975, as amended at 55 FR 11576, Mar. 29, 1990]

Subpart G—Specific Labeling Requirements for Specific Drug Products

§ 201.300 Notice to manufacturers, packers, and distributors of glandular preparations.

(a) Under date of December 4, 1941, in a notice to manufacturers of glandular preparations, the Food and Drug Administration expressed the opinion that preparations of inert glandular materials intended for medicinal use should, in view of the requirement of section 201(n) of the Federal Food, Drug, and Cosmetic Act (52 Stat. 1041; 21 U.S.C. 321(n)), be labeled with a statement of the material fact that there is no scientific evidence that the articles contain any therapeutic or physiologically active constituents. Numerous preparations of such inert glandular materials were subsequently marketed with disclaimers of the type suggested. The term *inert glandular materials* means preparations incapable of exerting an action or effect of some significant or measurable benefit in one way or another, i.e., in the diagnosis, cure, mitigation, treatment, or prevention of disease, or in affecting the structure or any function of the body.

(b) Manufacturers have heretofore taken advantage of § 201.100 permitting omission of directions for use when the label bears the prescription legend. Section 201.100(c) requires that the labeling of the drug, which may include brochures readily available to licensed practitioners, bear information as to the use of the drug by practitioners licensed by law to administer it. Obviously, information adequate for the use of an inert glandular preparation is not available to practitioners licensed by law.

(c) The Department of Health and Human Services is of the opinion that

inert glandular materials may not be exempted from the requirements of section 502(f)(1) of the act that they bear adequate directions for use; and, accordingly, that their labeling must include among other things, representations as to the conditions for which such articles are intended to be used or as to the structure or function of the human body that they are intended to affect. Since any such representations offering these articles for use as drugs would be false or misleading, such articles will be considered to be misbranded if they are distributed for use as drugs.

(d) The amended regulations provide also that in the case of drugs intended for parenteral administration there shall be no exemption from the requirement that their labelings bear adequate directions for use. Such inert glandular materials for parenteral use are therefore subject to the same comment as applies to those intended for oral administration.

§ 201.301 Notice to manufacturers, packers, and distributors of estrogenic hormone preparations.

Some drug preparations fabricated wholly or in part from estradiol and labeled as to potency in terms of international units or in terms of international units of estrone activity have been marketed. The international unit of the estrus-producing hormone was established by the International Conference on the Standardization of Sex Hormones at London, England, on August 1, 1932. This unit was defined as "the specific estrus-producing activity contained in 0.1 gamma (=0.0001 mg.) of the standard" hydroxyketonic hormone found in urine (estrone). The International Conference declared that it did not recommend the determination of the activity of nonhydroxyketonic forms of estrogenic hormones in units of estrone because of the varying ratios between the activity of such nonhydroxyketonic estrogenic hormones and estrone, when measured by different methods on test animals. There is no international unit for measuring the activity of estradiol and no accepted relationship between its activity and that of estrone, either in test animals or in humans. The dec-

laration of potency of estradiol in terms of international units or in terms of international units of estrone activity is therefore considered misleading, within the meaning of 21 U.S.C. 352(a). The declaration of the estradiol content of an estrogenic hormone preparation in terms of weight is considered appropriate.

§ 201.302 Notice to manufacturers, packers, and distributors of drugs for internal use which contain mineral oil.

(a) In the past few years research studies have altered medical opinion as to the usefulness and harmfulness of mineral oil in the human body. These studies have indicated that when mineral oil is used orally near mealtime it interferes with absorption from the digestive tract of provitamin A and the fat-soluble vitamins A, D, and K, and consequently interferes with the utilization of calcium and phosphorus, with the result that the user is left liable to deficiency diseases. When so used in pregnancy it predisposes to hemorrhagic disease of the newborn.

(b) There is accumulated evidence that the indiscriminate administration of mineral oil to infants may be followed by aspiration of the mineral oil and subsequent "lipoid pneumonia."

(c) In view of these facts, the Department of Health and Human Services will regard as misbranded under the provisions of the Federal Food, Drug, and Cosmetic Act a drug for oral administration consisting in whole or in part of mineral oil, the labeling of which encourages its use in pregnancy or indicates or implies that such drug is for administration to infants.

(d) It is also this Department's view that the act requires the labelings of such drugs to bear a warning against consumption other than at bedtime and against administration to infants. The following form of warning is suggested: "Caution: To be taken only at bedtime. Do not use at any other time or administer to infants, except upon the advice of a physician."

(e) This statement of interpretation does not in any way exempt mineral oil or preparations containing mineral oil from complying in all other respects